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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,197	GUTTERSON ET AL.	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *28-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04-08-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 04-08-2004 is acknowledged. The traversal is on the ground(s) that there is no evidence that the vector of Group II can be used in a method other than that of the methods of reducing expression of a target gene of Group I. Applicant points in particular to claim 4 and asserts that the other than to silence the expression of a gene comprising the 3'UTR there would be no use for the expression cassette of claim 31. Applicant further argues that the claims are all directed to specifically defined methods of reducing expression of a target gene in a cell using the specifically claimed constructs and therefore the Groups are not sufficiently independent to warrant restriction. Applicant argues that it would not be an undue burden to search two subclasses. This is not found persuasive because as discussed in the restriction, the vectors claimed can be used in a method materially different than the methods of reducing gene expression, as claimed, for example, for use in a method of generating an RNA for purification. Further, the constructs claimed only require at least portion of an NOS gene wherein an inverted repeat is present. The NOS promoter itself comprises and inverted repeat (see for example, Mitra et al., MGG (1989), 215, p 294-299), as do other portions of the NOS gene (no length is specified for such inverted repeat and, therefore, the inverted repeat could comprise as little as two base pairs), and the claimed vectors would encompass vectors used in many different types of methods, including methods wherein a gene is overexpressed, rather than depleted. Although Applicant is particularly concerned with

the relationship of claim 4 and 31, the inverted repeat of the NOS gene is actually heterologus to the target gene whose expression is reduced, so if Applicant is arguing that the vector of claim 31 is only useful in a method of reducing the expression of a target gene comprising the 3'-UTR, then the vector of claim 31 is not even useful in the method of claim 4, which reduces the expression of a gene heterologous to NOS. The vectors encompassed in claim 31 would include any vector comprising the NOS gene and any other portion of a gene or antisense sequence within a gene and, therefore, would include vectors used in many types of methods distinct from those of Group I. Although the distinct classes and subclasses listed in the restrict provided only two classes and subclasses, this is only representative of classes and subclasses searched for each Group and these particular classes and subclasses are very large. Further, the classification is not representative of the true search burden, as in this field the search is largely based in the scientific literature. The search for both inventions would constitute a burdensome search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 28-53 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04-08-2004.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a sequence having “substantial” identity to at least a subsequence of a target gene. The term "substantial" in claim 1 is a relative term which renders the claim indefinite. The term "substantial" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-27 are indefinite for the same reasons due to dependence on claim 1.

Claim 15 recites a sequence having “substantial” identity to a plant target gene. The term "substantial" in claim 1 is a relative term which renders the claim indefinite. The term "substantial" is not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 1-23 and 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing the expression of a target gene in a plant cell, does not reasonably provide enablement for methods of reducing expression of a target gene generally in any organism, particularly in a mammalian cell in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-23 and 26-27 are drawn broadly to methods of reducing the expression of a target gene in any cell, including a cell in vivo in a whole organism, including a mammal using an expression cassette comprising a sense or antisense targeting sequence and an inverted repeat of a NOS gene. The claimed methods would include use of the claimed methods for reduction of gene expression for any purpose, including, for example, methods wherein the reduction of expression creates a particular

phenotype or provides an in vivo response, including a therapeutic outcome. The specification provides one example wherein an expression cassette with and inverted repeat from the 3'-UTR of NOS and a sequence from polygalacturonase is expressed in a tomato plant and the expression of polygalacturonase is reduced in the plant. There are no examples wherein the claimed methods are used in non-plant cells, including any mammalian cells, in any setting in vitro or in vivo (cell culture or an animal), particularly wherein there is any reduction in gene expression sufficient to produce a phenotypic result or therapeutic outcome. The specification provides no guidance on vectors for use in non-plant cells, including mammals, nor does it provide any specific guidance on using the claimed methods in non-plant cells or organisms, including mammals.

At the time the instant Application was filed, and even to date, nucleic acid based methods were highly unpredictable, particularly when applied in mammals or, in the case of RNA interference, even in mammalian cells in culture. Applicant's propose a novel mechanism for their inhibition, using an unrelated RNA inverted repeat in concert with either a sense or antisense sequence related to the target gene. It is unclear what the exact mechanism is for the inhibition demonstrated by Applicant in plants, however, Applicant proposes that the mechanism is related to enzymes involved in RNAi responses. The enzymes involved in processing RNAi type inhibitors are different between plant cells and animal cells. At the time of the invention, the field of RNA interference was in its infancy and gene specific dsRNA inhibition in mammalian cells was also highly unpredictable, even in cells in culture, and the ability to inhibit gene

expression was variable and unpredictable among different cells lines and different target genes. (See for example, Caplen et al., Coburn et al. and Agami et al. for a review on the progression of RNA interference in mammalian cells.) Caplen et al. points out that, even post filing in 2003, "Many of the problems associated with developing RNAi as an effective therapeutic as the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system". Coburn et al. also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph), these issues of delivery and immune response problems would be applicable to the claimed methods, whether they use RNAi mechanism or any other mechanisms, and would apply to inhibition of a target gene for any purpose, therapeutic or to achieve a particular phenotype or other outcome (as encompassed in the claims).

In particular, in mammalian cells, dsRNA molecules were observed to cause the induction of the PKR response, resulting in cell apoptosis and non-specific mRNA expression inhibition. These sorts of reponses did not occur in plants and the results Applicant's observed in plants would not be expected to correlate with similar responses in animals or animal cells. In particular, the dsRNA portion of the nucleic acid used in the claimed methods is a bacterial element, which would be expected to provoke an immune response, as the dsRNA immune response was developed by mammalian cells

to combat invading DNA, including bacterial and viral sequences. Whatever the mechanism of inhibition, the introduction of dsRNA into mammalian cells (either in vitro or in vivo) would likely result in an unpredictable immune response. Examples in the literature demonstrate that in some organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. or Wianny et al.) Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the embryonic stage have demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions (see for example Wianny et al.). Further, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA in vivo (whole organism) and in Xenopus an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74).

The claimed methods require the delivery of a vector to express the dsRNA that mediates inhibition. Such methods were highly unpredictable for use in animals in vivo. Methods of inhibiting gene expression using nucleic acids in vivo (whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, including, for example, a reduction in a particular phenotype or inhibition of a target gene. Gene therapy methods have additional problems, not only with an inability to deliver the vectors, but additionally having problems with unpredictable immune responses and lack of an effective or sustained delivery, such that no effective inhibition

can be achieved. For example, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene are further hampered by unpredictable loss of expression (see for example Anderson, W.F. and Verma et al.). Verma et al. and Anderson do not make reference to DNA vector that express a dsRNA, as claimed, however, the methods claimed require that a vector expressing an RNA be delivered specifically to a target cell in an organism in vivo (whole organism) at a concentration effective enough to inhibit the expression of a target gene and at a concentration effective enough to inhibit the expression of a gene. At the time of the filing of the instant application, and even to date, in vivo systems for delivery of dsRNA and vectors expressing such were not available (see for example Agami, R., page 833; Scherr et al. page 52, second column). As such, although Verma et al. and Anderson discuss issues of delivery and expression in reference to gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. RNA interference methods additionally have problems with transient inhibition effects (see for example Agami, R.). The specification provides methods of inhibition in plants, however the methods of delivery of vectors in plants would not be feasible to apply in other organisms, particularly in mammals. Additionally, mammals have defense mechanisms that result in RNA degradation in vivo, as well as unpredictable immune responses precipitated by dsRNA, which do not occur in plants. The specification does not provide any guidance with respect to delivery of vectors expressing double stranded RNA molecules to a cell in vivo (whole organism) for organisms other than plants and the specification does not

provide specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of vectors to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid.

The specification does not provide the guidance required to overcome the art recognized unpredictability of the use of a dsRNA for inhibition in non-plant cells, including in mammalian cells or a mammal, or the art recognized problems for the delivery and expression of an RNA molecule from a vector in non-plant cells, including in mammalian cells in an animal. The guidance provided for the claimed methods in plant cells would not be expected to correlate with methods in non-plant cells because plants are not representative of mammalian cells in the processing of dsRNA, the immune response to dsRNA or in the types of vectors used or the delivery methods used. The field of nucleic acid based inhibition does not provide that guidance, such that the skilled artisan would be able to practice the claimed methods in organisms or cells other than plants. Therefore, the skilled artisan would not have been able to practice the broadly claimed methods of treating a mammal without undue, trial and error experimentation and, therefore, claims 1-23 and 26-27 are not enabled over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 7, 9-11, 13-19 and 21-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Mette et al. (EMBO Journal, Vol. 18, No. 1, p 241-248, 1999).

Mete et al. discloses methods wherein tobacco plants are transformed with a vector that comprises an inverted repeat sequence from an NOS gene and a targeting sequence with substantial identity to a sense sequence of a target gene heterologous to the inverted repeat under control of a CMV 35 S promoter, wherein expression of the target gene is reduced. The vector is circular and, therefore, the targeting sequence is both 5' and 3' to the inverted repeat. The inverted repeat disclosed in the vector of Mette et al. includes sequence from the coding, 5'-UTR region, terminator and 3'-UTR regions of the NOS gene and includes sense and antisense sequence and a linker region. Given the unclear nature of the term "substantial identity", the targeting sequence disclosed by Mette et al. would have "substantial identity" with plant genes, including plant pathogen genes. The targeting sequences disclosed by Mette et al. include sequence from the 5'-UTR, coding and 3'-UTR regions.

Therefore, Mette et al. anticipates claims 1-3, 6, 7, 9-11, 13-19 and 21-24.

Claims 1-3, 6, 8-19, 21, 24, and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Waterhouse et al.

Waterhouse et al. disclose methods wherein cells, including plant cells, are transformed with vectors to reduce the expression of a target gene. These vectors comprise a subsequence of the target gene, including a sense sequence, and further include a ribozyme sequence, which comprises an antisense subsequence of the target gene. The subsequence of the target gene is under control of a promoter, including the Agrobacterium sp. NOS gene promoter (see for example, column 16), which comprises an inverted repeat from the NOS gene (as evidence by Mitra et al.), which comprises a sense and antisense sequence connected by a linker. Waterhouse et al. disclose their methods as used to reduce the expression of plant genes, including plant pathogen genes, such as plant viral genes, and in plants that include, for example, wheat, rice, cotton, sugarbeet, soybean, and tomato (see column 21).

Therefore, Waterhouse et al. anticipates claims 1-3, 6, 8-19, 21, 24, and 25.

Claims 1,4, 9, 11, 15, 16, 17, 20, 21 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Baulcombe et al. (US Paten No. 6,753,139).

Baulcombe et al. disclose methods of post-transcription gene silencing, wherein cells are transformed with a vector comprising a sense copy of a gene under control of a promoter, wherein the promoter includes the NOS promoter, which inherently includes an inverted repeat sequence from the NOS gene, as evidenced by Mitra et al.). Baulcombe disclose wherein the targeted gene is polygalacturonase from toato (see for example, column 3)

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Brummell et al. Inverted repeat of a heterologous 3'-untranslated region for high-efficiency, high-throughput gene silencing. The Plant Journal, February 2003, Vol. 33, No. 4, p 793-800.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (571) 272-0759. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Lacourciere
June 25, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER